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# Transports of Delight

**Intrinsic optical signals, evoked by neural activity, provide an essentially noninvasive means of monitoring the organization of brain circuitry. A new study by Gurden et al. in this issue of *Neuron* reveals a surprising role of astrocyte glutamate transporters in generating these signals.**

Neuronal activity generates small changes in the intrinsic optical properties of CNS tissue. When imaged, even through the (thinned) skull, these can be used to map which parts of the cortex, or other exposed brain area, are active (Grinvald et al., 1986). Use of this functional imaging technique has allowed the discovery of novel features of cortical organization (Bonhoeffer and Grinvald, 1991), yet the cellular basis of the signals is poorly understood, with altered light scattering, changes of hemoglobin oxygenation, and increases of blood volume all thought to contribute to the signals (Frostig et al., 1990; Aitken et al., 1999; Meister and Bonhoeffer, 2001). Despite the common assumption that it is neuronal activity that is being imaged, in this issue of *Neuron*, Gurden et al. (2006) report a surprising involvement of astrocytes in generating odor-evoked intrinsic optical signals in the olfactory bulb in vivo.

Odor stimulation leads to action potentials arriving at the olfactory receptor neuron axon terminals within the olfactory bulb (see Figure 5 of Gurden et al., 2006). Here, $Ca^{2+}$ influx releases glutamate from the axon terminals, activating postsynaptic NMDA, AMPA, and metabotropic glutamate receptors on mitral and tufted cells (the principal output cells of the glomerulus), as well as NMDA and AMPA receptors on local interneurons. The resulting spatially localized component of the activity-evoked intrinsic optical signals was found to be inhibited, as expected, by TTX, and also inhibited when glutamate release was reduced by activating the presynaptic dopamine and $GABA_B$ receptors on the axon terminals, which are normally stimulated by local interneuron activity. Thus, action potential-evoked glutamate release initiates the intrinsic optical signals. One might imagine that activation of postsynaptic neurons, leading to downstream cell swelling, increased cell metabolism, and activation of increased blood flow would then generate the optical signals. However, Gurden et al. (2006) found that the signals were not affected by blocking AMPA and NMDA receptors, nor by blocking mGluR receptors (although, since all three receptor classes were not blocked together, this leaves open the possibility that activation of either ionotropic receptors alone or metabotropic receptors alone generates sufficient postsynaptic excitation to produce the intrinsic optical signals).

Surprisingly, applying TBOA to block glutamate transporters, which are located mainly in astrocytes, reduced the optical signals by about two-thirds. (TBOA also reduced electrically evoked field potentials by a similar factor, probably because blocking transporters leads to glutamate accumulating and desensitizing AMPA receptors). TBOA is a nonspecific blocker of all $Na^+$-dependent glutamate transporters. Since olfactory glomeruli express two glial glutamate transporters, GLAST and GLT1, with different spatial locations (Utsumi et al., 2001), it would be interesting to use the specific GLT1 blocker dihydrokainate to determine which transporter is the main mediator of the optical signals.

How could activation of astrocyte glutamate transporters generate intrinsic optical signals? An obvious possibility is that light scattering is altered as a result of astrocytes swelling when glutamate is taken up (Schneider et al., 1992). This swelling occurs partly because glutamate transporters take up each glutamate anion with the movement of three $Na^+$ and one $H^+$ into the cell, while one $K^+$ moves in the other direction on the transporter and two more $K^+$ will exit through ion channels to maintain charge neutrality: since $H^+$ is osmotically inactive, effectively, four ions move in but only three move out, and the excess ion entry will be followed by osmotic water movement. In addition, there may be water transported by the glutamate transporter itself.

Intrinsic optical signals may also be partly due to the increase of blood flow and altered hemoglobin oxygenation associated with neuronal activity and resulting metabolic activity. If this is true in the olfactory bulb, then the data of Gurden et al. (2006) will also be relevant in understanding how the functional imaging signals used in BOLD and PET experiments are generated, since these also depend on neural activity evoking an increase in blood flow. However, although astrocytes have been shown to increase blood flow in response to neural activity (Zonta et al., 2003; Takano et al., 2006), this is mediated via mGluR and AMPA receptors, which Gurden et al. (2006) show are not involved in generating the optical signals in the olfactory bulb. Furthermore, for the spatially restricted responses studied by Gurden et al. (2006), it seems that, for the 630 nm illumination wavelength used, most of the intrinsic optical signal is generated by light scattering rather than by blood-related signals (Meister and Bonhoeffer, 2001).

It will be important to examine the wavelength dependence of the transporter-mediated optical signals to assess the relative contribution of light scattering and blood-related signals (Meister and Bonhoeffer, 2001). If it turns out that astrocyte glutamate uptake does induce an optical signal related to increased blood flow or metabolism, how might this occur? Two possibilities spring to mind. First, glutamate uptake into astrocytes consumes ATP to restore the ion gradients driving uptake and to power the intracellular conversion of the glutamate to glutamine. However, this is a relatively small fraction of the signaling-evoked ATP usage in the CNS (<3%: Attwell and Laughlin, 2001), suggesting that astrocyte metabolic changes are unlikely to be a major cause of alterations in hemoglobin oxygenation. Second, glutamate uptake will depolarize astrocytes slightly, and this will cause $K^+$ ions to flow out across the parts of astrocyte membranes that have the highest density of $K^+$ channels, i.e., the endfeet apposed to blood vessels, where they may cause dilation of arteriolar smooth muscle and increase blood flow (Paulson and Newman, 1987). If this speculative mechanism for increasing blood flow does exist, then in the olfactory glomerulus the increase of blood flow would reflect the activity of both the incoming olfactory signal and the response of the postsynaptic mitral/tufted cells, since the glutamate transporter current generated in glomerular astrocytes reflects glutamate release both from the olfactory receptor axon terminals and from the dendrites of the mitral/tufted cells (De Saint Jan and Westbrook, 2005).

This work is important for further highlighting the importance of astrocytes in generating signals that allow us to monitor brain activity relatively noninvasively. Just as activation of astrocyte metabotropic glutamate receptors contributes to the increase in cerebral blood flow that underlies BOLD and PET imaging signals (Zonta et al., 2003; Takano et al., 2006), activation of their glutamate transporters is now shown to contribute to intrinsic optical imaging.

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